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Evaluation of Preoperative Short Course Intensity Modulated Radiation Therapy in Treatment of Locally Advanced Rectal Carcinoma

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ABSTRACT

Background: The optimal RT fractionation and the timing of surgery in resectable locally advanced rectal carcinoma is still debatable. Postponing the time of surgery after SCRT seems to be more beneficial in inducing down-staging, and reducing postoperative morbidity than SCRT with immediate surgery. IMRT is used successfully in many cancers helping to achieve better conformality.

Aim of work: The study aimed to evaluate the efficacy and tolerability of preoperative short-course IMRT with delayed surgery in patients with resectable locally advanced rectal carcinoma.

Patient and Methods: Patients with resectable locally advanced rectal carcinoma were treated with preoperative short-course IMRT (25 Gy over 5 fractions) followed by surgery after 4-8 weeks.

Results: 37 patients were included, down-staging was observed in 54.1% of them; patients with cN2 disease, radiological EMVI, and radiologically involved mesorectalfacia (MRF) tend to have a statistically significant less down-staging. severe early and late toxicity was reported in 5.4% and 8.1% of the patients respectively, and 37 % had postoperative complications. 33 patients (94.6%) had curative surgery, 9% had pCR, and sphincter sparing was achieved in 28% of patients with low rectal tumors. Cumulative 2 years DFS and OS were 71 % and 80 % respectively.

Conclusion: SCRT with delayed surgery is a valid convenient, safe, and economically beneficial option in the treatment of locally advanced resectable rectal carcinoma, utilization of IMRT can help in reducing the dose to organs at risk. Further studies with a larger number of patients are mandatory to identify the most suitable patients for this approach.

Keywords:*Resectable locally advanced rectal carcinoma; Short-course radiotherapy with delayed surger;IMRT.*

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INTRODUCTION

Neoadjuvant radiotherapy (RT) is frequently used in the treatment of locally advanced rectal carcinoma trying to achieve down-staging, sphincter preservation, as well as improvement in local control (LC) or even survival.[1,2] There is still a debate on the optimal fractionation of RT, the timing of surgery, and the utilization of concurrent chemotherapy.[3]

Conventionally fractionated concurrent chemoradiotherapy (CCRT); (1.8–2 Gy ×25–28 fractions) followed by surgery after 4-8 weeks is the most commonly used approach. [4-7]This interval gives time for recovery from early toxicity and allows for down-staging, and achieving a pathological complete response (pCR).[4,6,7,8,9,10]

However, it increases morbidity, and, in some trials, mortality.[11,12]

Short-course radiotherapy (SCRT) with immediate surgery; 25 Gy over 5 fractions and surgery within the following week has been commonly used in Sweden and some other countries in Northern and Western Europe. [4,5,6,7]

Many trials have examined the most appropriate treatment schedule during the last 2 decades, Polish and Australian trials compared long-course CCRT with SCRT with immediate surgery,[14,15]no significant differences were observed in postoperative complications, LC, late toxicity, or survival; nevertheless, a significantly lower acute radiation toxicity was observed with SCRT.

Postponing the time of surgery after SCRT also seems to be beneficial in inducing down-staging, pCR, and reducing postoperative morbidity than SCRT with immediate surgery, however. it did not increase the rate of sphincter-saving procedures and curative surgery.[16,17,18,19]

Traditionally, pre-operative RT has been delivered via three-dimensional conformal RT (3D-CRT) with three or four-field techniques for rectal cancer. More advanced techniques have been widely and successfully used for head-and-neck, prostate, and other cancers, such as intensity-modulated radiotherapy (IMRT),[20,21]however, its potential clinical benefits remain debatable in rectal cancer.[22]

The study aimed to evaluate the efficacy and tolerability of preoperative short-course IMRT with delayed surgery in patients with resectable locally advanced rectal carcinoma.

PATIENTSAND METHODS

The current work is a prospective study, including patients with a pathologically confirmed diagnosis of rectal carcinoma, in Clinical Oncology and Nuclear Medicine Department, El Hussein Hospital, Faculty of Medicine, Al-Azhar University during the period between June 2016 and August 2018. Approval of the ethical committee and written informed consent from every patient was obtained.

Eligibility criteria:

- Resectable locally advanced rectal adenocarcinoma; clinical stage II-III.
- Age more than 18 years and less than 80 of both genders.
- Performance Status ≤ 2 ECOG scale.
- Ejection fraction > 55%.
- Adequate laboratory investigations.
- Medically fit for surgery.
- Patients without any primary treatment for their current disease (surgical, chemotherapy, or radiotherapy).

Ineligibility Criteria:

- Tumors extending above 15 cm from the anal verge.
- Pregnant women.
- Patients with synchronous tumors of the colon.
- Patients with a history of malignancy except for basal cell carcinoma.
- Patients presented with intestinal obstruction.
- Obese patients (> 120 kg).
- Severe skeletal deformity or any disease interfering with patient alignment and positioning for radiation therapy delivery.

All patients were subjected to clinical examination, colonoscopy, CT chest, abdomen and pelvis, Pelvic MRI with a series of laboratory investigations to assess the extent of disease and the presence of co-morbidity if any.

Staging of the disease was assessed according to the AJCC cancer staging system the 7th edition,[23] and the ECOG scale was used to assess the performance status.[24]

Tumors were classified regarding the distance of the lower extent of the primary tumor from anal verge into:

High: > 10 cm.
Middle: > 5 cm and ≤ 10 cm.
Low: ≤ 5 cm.
Mesorectalfacia (MRF) was considered involved when the distance of the tumor to the MRF of ⩽1 mm.

Trial design:
In this prospective study, patients were planned to receive preoperative short course IMRT (25 Gy / 5 fractions in 5 consecutive days), then total mesorectal excision (TME) was planned 4-8 weeks after completion of neoadjuvant treatment. Target volumes and organs at risk were defined according to Radiationtherapy Oncology Group (RTOG) Consensus Panel Contouring Atlas. [25,26]

An IMRT plan designed to cover 98 % of PTV with 95 % of the treatment dose while delivering 105% of the treatment dose to below 10%, and not delivering ≥110% of the treatment dose to the PTV. We kept the maximal irradiation dose of the bladder under 24 Gy, bowel under 25 Gy, and femur heads under 20 Gy and kept the D50% of the above 3 organs at risk (OARs), irradiated ≤20 Gy, ≤13 Gy, and ≤15 Gy respectively.

Plans were generated concerning delivery using only 6-MV photons via linear accelerator (Varian Medical System). PTV coverage had been given the highest priority, then minimization of dose to bowel while the intermediate priority for reducing the dose to the bladder, and femoral head/neck. Quality assurance (QA) was done before starting treatment for every case, verification with an electronic portal image device (EPID) was done before every fraction.

Acute and late radiotherapy adverse effects were graded according to RTOG/EORTC radiation toxicity grading.[27]

Response evaluation:

Abdominopelvic CT, MRI pelvis and colonoscopy were done for all cases about one week before surgery. A tumor and/or nodal down-staging is considered when ycT and/or ycN is lower than cT and/or cN as defined by MRI, while clinical CR represented the absence of tumor by clinical examination, MRI, and colonoscopy.

Surgery:

TME (Total mesorectal excision) was planned 4-8 weeks after the completion of radiotherapy, and choice between low anterior resection and abdominoperineal resection and whether a temporary colostomy should be performed was left to the surgeon's discretion.

Surgery was considered adequate if achieving R0 resection (absence of macroscopic or microscopic

residual disease), while pCR was considered when no malignant cells are observed in the surgical specimen.

Post-operative complications were the reported complication occurring within one month from surgery.

Adjuvant treatment:

Following wound healing, patients received six months of adjuvant chemotherapy either FOLFOX-4 regimen or Degramont regimen, the selection was based on the stage of the disease and the expected patient tolerance.

Follow up:
After finishing adjuvant chemotherapy regimen patients had scheduled visits with investigations (CEA every 3 months, CT scan every 6 months, and colonoscopy in 1 year, then every 2–3 years if negative).
Disease-free survival (DFS) was the time from surgery to confirmed local recurrence, distant metastases, or death whichever occurred first, patients who neither relapsed nor died were censored at last assessment before a loss to follow-up.
Overall survival was the time from diagnosis till death, with survivors being censored at the time of the last follow-up. Living patients or patients lost to follow-up were censored on the last known alive date.

Statistical Methods:

Statistical presentation and analysis of this study were conducted via SPSS V22, using the mean, standard deviation, student t-test, chi-square, linear correlation coefficient, and analysis of variance [ANOVA] tests, survival analysis was done using Kaplan-Meier method, and the p-value was considered significant if ≤ 0.05.

RESULTS

The current prospective study included 37 patients with a pathologically confirmed diagnosis of locally advanced resectable rectal adenocarcinoma fulfilling the eligibility criteria. Table (1) demonstrates the clinicopathologic features of the patients.

The whole study group received preoperative IMRT 25 Gy / 5 fractions over 5 consecutive days without any interruptions. PTV coverage, doses received by OAR, homogeneity index, and conformity index are shown in table (2)

Down-staging was observed in 20 patients (54.1%); it was noticed that 4 patients (10.8%) had a clinical CR, 16 patients (43.2%) had a partial response (PR), 15 patients (40.5%) had stable disease (SD) while 2 patients (5.4 %) had disease progression (PD). Factors affecting clinical down-staging are shown in table (3).

It was noticed that patients with cN2 disease, radiological EMVI, and radiologically involved mesorectalfacia (MRF) tend to have a poor clinical response with statistically significant *P-values*.

Only 35 patients (94.6%) submitted to surgery while one patient (2.7 %) refused surgery as she achieved clinical CR and the other one (2.7 %) was unfit for surgery.

The median period between radiotherapy and surgery was 7.3 weeks (range of 4.3-8 weeks), Curative surgery was done in 33 patients (94.3%) only; 17 of them (51.5%) had an anterior resection and the remaining 16 patients (48.5%) had APR. On the contrary, 2 patients had laparotomy only but the tumor was found to be irresectable. For patients having low rectal tumors at presentation (25 patients), sphincter sparing was successfully achieved in 7 of them (28%).

Histopathological examination and pathological TNM staging were done; histopathology evaluation results are shown in table (4).

All the 33 patients who submitted to curative surgery received adjuvant chemotherapy; 26 patients (78.8%) received the FOLFOX-4 regimen while 7 patients (21.2%) received the Degramont regimen, which was given to patients who experienced pCR and patients who were not expected to tolerate FOLFOX-4 regimen.

Most of the patients tolerated radiotherapy well, as no patients suffered from grade III or IV hematological toxicity, and no grade IV non-hematological toxicity was reported.

Only two patients (5.4%) had grade III early skin toxicity with no reported late skin effects, no patients suffered from GIII early bowel or bladder toxicity on the contrary GIII late bowel and bladder toxicity was reported in 5.4% and 2.7% respectively, table (5).

Surgical complications were reported in 37 % (13/35) of the operated patients, wound infection was the most frequently reported surgical complication and it occurred in 14.2% (5/35) of the patients; three of them (60%) were submitted to APR, the next most frequent complication was delayed wound healing and it was reported in 11.4% (4/35) of the patients; three of them (75%) also were submitted to APR, table (6).

Only 33 patients who submitted to R0 resection were evaluated for PFS and OS; The median follow up period was 23 months, by the end of this study, 6 patients (18.2%) died and 27 patients (81.8%) were still alive.

9% of the patients (3/33) suffered from a locoregional recurrence, 21.2% (7/33) had distant metastasis while 6% (2/33) had simultaneous systemic and locoregional recurrences.

The liver was the common partner in all cases with distant metastasis as it was reported in all the seven patients (100%) with distant metastasis, then lung, para-aortic lymph nodes and bone with 2 cases

(28.6%) for each of them and the lowest was the skin which was present only in one patient (14.3%).

Age	**Range**	22-72	
	Mean ±SD	14.956	
		N (37)	**%**
Age group	<40 Years	10	27.00
	≥40 Years	27	73.00
Gender	Male	20	54.05
	Female	17	45.95
Family history	positive	3	8.11
	negative	34	91.89
Comorbidity	HTN	7	18.92
	DM	7	18.92
	HCV positive	3	8.11
	COPD	2	5.41
Smoking	Smokers	7	18.92
	Non smokers	30	81.08
Performance Status	0	3	8.11
	I	24	64.86
	II	10	27.03
Clinical presentation	Bleeding per rectum	34	91.89
	Constipation	18	48.65
	Pelvic pain	18	48.65
	Change of bowel habits	10	27.03
	Loss of weight	7	18.92
Initial Tumor marker	High	34	91.89
	Normal	3	8.11
Tumor Site	Low	25	67.57
	Middle	8	21.62
	High	4	10.81
Histopathology	Adenocarcinoma	30	81.08
	Mucinous	4	10.81
	Signet ring	2	5.41
	Undifferentiated carcinoma	1	2.70
Grade	I	3	8.11
	II	22	59.46
	III	11	29.73
	IV	1	2.70
Pretreatment clinical tumor staging(cT)	2	9	24.32
	3	26	70.27
	4	2	5.41
Pretreatment clinical nodal staging(cN)	0	4	10.81
	1a	6	16.22
	1b	16	43.24
	2a	4	10.81
	2b	7	18.92
Pretreatment clinical stage group	IIA	4	10.81
	IIIA	8	21.62
	IIIB	19	51.35
Radiological Extramural vascular invasion (EMVI)	Yes	7	18.92
	No	30	81.08
Radiological mesorectal fascia (MRF) involvement	Positive	6	16.22
	Negative	31	83.78

Table 1: The clinicopathologic characteristics of the study group.

Parameter		Value
		Mean ±SD
PTV volume		1588 ± 277 cc
PTV mean dose		25.45 ± 0.19
Dmax (Gy)		26.57 ± 0.29
Dmin (Gy)		20.6 ± 1.47
D98%		24.49 ± 0.22 Gy
D50%		25.49 ± 0.21 Gy
D2%		26 ± 0.23 Gy
HI		0.059 ± 0.01
CI		0.98 ± 0.04
Bowel volume		947.46 ± 320.41 cc
Bowel mean dose		11.31 ± 1.79 Gy
Bowel V25 Gy	Volume (cc)	15.50 ± 25.22
	Percentage (%)	1.450% ± 2.732
Bowel V22.5 Gy	Volume (cc)	66.98 ± 62.25
	Percentage %	6.890% ± 5.722
Bowel V20 Gy	Volume (cc)	118.64 ± 82.11
	Percentage %	12.259% ± 6.937
Bowel V17 Gy	Volume (cc)	193.80 ± 115.40
	Percentage %	19.870% ± 8.733
Bowel V15 Gy	Volume (cc)	263.24 ± 143.32
	Percentage %	27.373% ± 10.916
Bowel V10 Gy	Volume (cc)	508.70 ± 180.59
	Percentage %	54.054% ± 11.352
Bowel V5 Gy	Volume (cc)	714.34 ± 234.74
	Percentage %	76.173% ± 8.600
Urinary bladder volume		278.47 ± 232.84 cc
Urinary bladder mean dose		20.5 ± 2.4 Gy
Rt. Femoral head mean dose		10.67 ± 1 Gy
Lt. Femoral head mean dose		10.55 ± 1.14 Gy
Bone marrow volume		1374 ± 178.2 cc
Bone marrow mean dose		13.63 ± 1.6Gy

Table 2: Radiotherapy parameters.

		Clinical down staging				T-Test	
		Yes		No			
		Mean ± SD		Mean ± SD		t	P-value
Age		50.450 ± 13.694		48.000 ± 16.647		0.491	0.626
Duration of Symptoms (Months)		3.450 ± 2.523		4.382 ± 3.257		-0.981	0.333
Period from diagnosis to RT (Days)		11.200 ± 3.286		13.412 ± 6.847		-1.283	0.208
Period from radiotherapy to surgery (Weeks)		7.078 ± 1.048		6.929 ± 0.905		0.447	0.658
		Clinical down staging					
		Yes		No		Chi-Square	
		N	%	N	%	X^2	P-value
Age group	<40 Years	5	25.00	5	29.41	0.091	0.763
	≥40 Years	15	75.00	12	70.59		
Sex	Male	11	55.00	9	52.94	0.016	0.900
	Female	9	45.00	8	47.06		
Family history	Yes	0	0.00	3	17.65	1.837	0.175
	No	20	100.00	14	82.35		
Smoking	Yes	4	20.00	3	17.65	0.033	0.855
	No	16	80.00	14	82.35		
Performance Status	0	2	10.00	1	5.88	1.164	0.559
	I	14	70.00	10	58.82		
	II	4	20.00	6	35.29		
Initial Tumor marker	High	19	95.00	15	88.24	0.564	0.452
	Normal	1	5.00	2	11.76		
Tumor site	High	1	25.00	3	75.00	2.954	0.184
	middle	3	37.50	5	62.50		
	Low	16	64	9	36		
Histopathology	Adeno	18	90.00	12	70.59	5.996	0.112
	Mucinous	0	0.00	4	23.53		
	Signet ring	1	5.00	1	5.88		
	Undifferentiated	1	5.00	0	0.00		
Grade	I	2	10.00	1	5.88	1.372	0.712
	II	12	60.00	10	58.82		
	III	5	25.00	6	35.29		
	IV	1	5.00	0	0.00		
Pretreatment clinical tumor staging(cT)	T2	3	15.00	6	35.29	5.253	0.072
	T3	17	85.00	9	52.94		
	T4	0	0.00	2	11.76		
Pretreatment clinical nodal staging(cN)	N0-1	17	85.00	9	52.94	4.521	0.033*
	N2	3	15.00	8	47.06		
Pretreatment clinical stage group	IIA	4	20.00	0	0.00	6.943	0.074
	IIIA	4	20.00	4	23.53		
	IIIB	11	55.00	8	47.06		
	IIIC	1	5.00	5	29.41		
Radiological Extramural vascular invasion (EMVI)	Yes	1	5.00	6	35.29	5.498	0.019*
	No	19	95.00	11	64.71		
Radiological mesorectal fascia (MRF) involvement	Positive	1	5.00	5	29.41	4.031	0.045*
	Negative	19	95.00	12	70.59		

Table 3: Factors affecting clinical down staging:

		N (35)	%
Histopathology	Adenocarcinoma	28	80
	Mucinous	4	11.4
	Signet ring	2	5.7
	Undifferentiated carcinoma	1	2.9
Grade	I	3	8.6
	II	21	60
	III	10	28.6
	IV	1	2.9
Pathological primary tumor assessment (ypT)	T0	3	8.57
	T1	1	2.86
	T2	15	42.86
	T3	14	40.00
	T4	2	5.71
Pathological nodal assessment (ypN)	No	10	28.57
	1a	6	17.14
	1b	8	22.86
	2a	3	8.57
	2b	8	22.86
Pathological stage	pCR	3	8.57
	I	5	14.29
	IIA	2	5.71
	IIIA	9	25.71
	IIIB	8	22.86
	IIIC	8	22.86
Pathological perineural invasion (PNI)	Yes	5	14.3
	No	30	85.7
Pathological lymphovascular invasion (LVI)	Yes	4	11.4
	No	31	88.6
Presence of tumor necrosis	Complete necrosis	3	8.57
	Partial necrosis	23	65.71
	No Necrosis	9	25.71

Table 4: Histopathology evaluation results.

Toxicity		**G I**	**G II**	**G III**	**G IV**	**G V**
Hematological						
Anemia		1(2.7%)	2(5.4%)	0	0	0
Neutropenia		3(8.1%)	1(2.7%)	0	0	0
Thrombocytopenia		0	0	0	0	0
Non-hematological						
Skin	Early	19(51.35%)	6(16.22%)	2(5.4%)	0	0
	Late	0	0	0	0	0
Bowel	Early	13(35.14%)	3(8.11%)	0	0	0
	Late	4(10.81%)	0	2(5.4%)	0	0
Bladder	Early	14(37.84%)	1(2.70%)	0	0	0
	Late	2(5.41%)	1(2.70%)	1(2.7%)	0	0

Table 5: Neoadjuvant RT related toxicity.

Surgical complications	Number	Percentage
Delayed wound healing	4	11.4 %
wound infection	5	14.2 %
Urinary bladder injury	1	2.86 %
Fistula	1	2.86 %
DVT	1	2.86 %
Abdominal dehiscence	1	2.86 %

Table 6: Surgical complications.

The median DFS and OS have not been reached. The cumulative 1 year and 2 years DFS were 88 % and 71 % respectively, while the cumulative 1 year and 2 years OS were 90.1% and 80 % respectively, Figures (1&2).

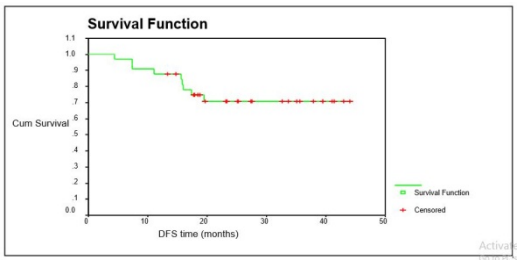

Fig. 1: Disease free survival.

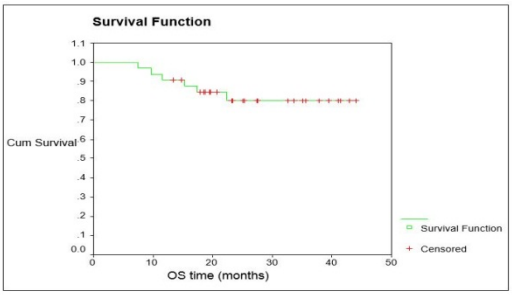

Fig. 2: Overall survival.

Factors affecting DFS and overall survival were studied, (Table 7,8). It was found that patients younger than 40 years old and patients with ypN2 stage have significantly worse PFS but there was no significant impact on OS, on the other hand, other prognostic variables Showed no statistically significant effect on either PFS or OS.

DISCUSSION

The optimal RT fractionation, concomitant chemotherapy, and the proper timing of surgery in patients suffering from locally advanced resectable rectal carcinoma has been much debated.

The general idea of the current prospective study was to explore the safety of SCRT with delayed surgery and its efficacy to induce Down-staging, pCR, sphincter preservation, and the impact of utilizing IMRT in reducing the dose to OAR.

SCRT followed by immediate surgery, doesn't induce down-staging, [28]but a longer period between RT and surgery leads to a higher down-staging rate (44.2% vs. 13%).[19]Moreover, a Swedish retrospective study reported that 74 % of the patients had tumor regression on MRI after a median of 4 weeks after the completion of RT but it was noticed that only 55.4 % of the patients had MRI reassessment.[29]

In our study the rate of down-staging was 54.1%, It was noticed that patients with cN2 disease, radiological EMVI, and radiological involved mesorectalfacia (MRF) tend to have a statistically significant worse clinical down-staging.

A Korean study showed a higher conformal radiation dose to the target and significantly reduced the dose to OAR when using short course IMRT compared to the four-box field (3D-CRT),[30] our study results were consistent regarding PTV coverage and femoral head mean dose but Bowel and bladder mean doses were higher than those reported in the IMRT arm but still better than the conformal radiotherapy results, the difference may be attributed to the utilization of tomotherapy in the Korean study.

In our study, severe early and late toxicity were reported in 5.4% and 8.1% of the patients respectively, Polish trial reported that the incidence of severe early and late adverse effects in SCRT arm was 3.2 % and 10.1% respectively.[14]

Stockholm III trial reportedsevere acute toxicity in <1% of the patients receiving SCRT with immediate surgery group, 4.2 % of the patients in SCRT with delayed surgery group and 5 % in the CCRT group, and it was thought that acute radiation toxicity was masked by surgical complications in the SCRT with immediate surgery group. [17]

A retrospective study including patients who received SCRT then delayed surgery, Severe radiation-induced toxicity was reported in 5.4 % of them.[29]

Polish trial demonstrated that the rates of postoperative complications for the SCRT with immediate surgery group and the long course CCRT group were 27% vs 21%, respectively but it was noticed that only 39 % of the patients had APR.[31]

In an older Dutch trial, it was noticed that patients who had an abdominoperineal resection, after preoperative RT had more perineal complications than those assigned to surgery alone 26 % vs. 18 %.[32]

Stockholm III trial showed a significantly lower incidence of postoperative complications in the SCRT followed by delayed surgery vs. SCRT with immediate surgery, (41 % vs. 53%).[17]

In our study, postoperative complications were reported in 37 % of the patients and it was obvious that most of them had APR.

It is suggested that patients with a pCR might have better DFS and OS.[10] In our study, we reported a pCR rate of 9%, and it was consistent with the results of a retrospective study held in the Netherlands that found a significantly lower pCR rate in patients treated with SCRT with delayed surgery compared to long course CCRT (9.3% vs. 17.5% respectively).[18]

Stockholm III trial reported a pCR rate of 11.8% in patients receiving SCRT with delayed surgery.[16]

		DFS				T-Test or ANOVA	
		N	Mean	±	SD	T or F	P-value
Age group	<40 Years	9	18.167	±	10.940	-2.055	0.048*
	≥40 Years	24	26.929	±	10.898		
Gender	Male	18	22.022	±	11.260	-1.405	0.170
	Female	15	27.560	±	11.293		
Family history	Yes	2	18.500	±	19.940	-0.765	0.450
	No	31	24.929	±	11.130		
Performance Status	0	3	30.867	±	11.418	1.306	0.286
	I	22	25.477	±	10.120		
	II	8	19.588	±	14.366		
Smoking	Yes	5	19.740	±	9.215	-1.019	0.316
	No	28	25.396	±	11.732		
Initial Tumor marker	High	30	23.993	±	11.235	-0.863	0.395
	Normal	3	30.000	±	14.703		
Site	Low	22	27.759	±	10.421	2.363	0.122
	Middle	7	31.843	±	11.629		
	High	4	32.550	±	7.188		
Histopathology	Adenocarcinoma	28	26.268	±	10.584	1.524	0.229
	Mucinous	3	15.833	±	17.270		
	Signet ring	1	15.800	±	0.000		
	Undifferentiated	1	11.000	±	0.000		
Grade	I-II	24	26.817	±	10.439	1.946	0.061
	III-IV	9	18.467	±	12.394		
Pretreatment clinical tumor staging(cT)	T2	9	29.644	±	12.051	1.293	0.289
	T3	23	22.761	±	11.072		
	T4	1	19.500	±	0.000		
Pretreatment clinical nodal staging(cN)	N0-1	24	26.558	±	10.744	1.703	0.099
	N2	9	19.156	±	12.134		
Pretreatment clinical stage group	IIA	3	29.767	±	13.210	1.600	0.211
	IIIA	8	30.050	±	11.851		
	IIIB	18	22.867	±	10.058		
	IIIC	4	17.125	±	13.473		
Radiological Extramural vascular invasion (EMVI)	Yes	5	21.260	±	8.968	-2.150	0.289
	No	28	26.732	±	10.821		
Radiological mesorectal fascia (MRF) involvement	Positive	4	19.600	±	11.867	-0.919	0.365
	Negative	29	25.221	±	11.430		
Overall clinical down staging	**Yes**	15	22.840	±	10.768	0.328	0.723
	No	15	26.293	±	13.141		
	CR	3	24.267	±	5.514		
Pathological tumor assessment (pT)	T0	3	24.267	±	5.514	0.543	0.706
	T1	1	23.200	±	0.000		
	T2	15	27.700	±	11.634		
	T3	13	21.446	±	12.695		
	T4	1	19.500	±	0.000		
Pathological nodal assessment (pN)	N0-1	24	27.350	±	10.631	2.483	0.019*
	N2	9	17.044	±	10.588		
Pathological stage	pCR	3	24.267	±	5.514	1.264	0.308
	I	5	24.580	±	14.617		
	IIA	2	29.100	±	14.566		
	IIIA	9	29.733	±	10.027		
	IIIB	8	24.550	±	10.980		
	IIIC	6	15.317	±	11.142		
Pathological perineural invasion (PNI)	Yes	5	19.740	±	9.215	-1.019	0.316
	No	28	25.396	±	11.732		
Pathological lymphovascular invasion(LVI)	Yes	4	22.260	±	9.948	-2.008	0.231
	No	29	26.732	±	10.821		
Presence of tumor necrosis	Complete necrosis	3	24.267	±	5.514	0.200	0.820
	Partial necrosis	23	25.313	±	11.174		
	No Necrosis	7	22.114	±	14.882		

Table 7: Disease free survival and its relation to the prognostic factors.

		OS				T-Test or ANOVA	
		N	Mean	±	SD	T or F	P-value
Age group	<40 Years	9	20.378	±	9.317	-1.860	0.072
	≥40 Years	24	27.692	±	10.309		
Gender	Male	18	23.211	±	10.158	-1.529	0.136
	Female	15	28.680	±	10.317		
Family history	Yes	2	22.100	±	14.849	-0.497	0.623
	No	31	25.929	±	10.394		
Performance Status	0	3	30.867	±	11.418	1.025	0.371
	I	22	26.459	±	9.284		
	II	8	21.663	±	13.067		
Smoking	Yes	5	20.860	±	9.245	-1.129	0.267
	No	28	26.561	±	10.557		
Initial Tumor marker	High	30	25.267	±	10.164	-0.743	0.463
	Normal	3	30.000	±	14.703		
Site	Low	22	27.141	±	9.484	4.719	0.117
	Middle	7	32.957	±	10.085		
	High	4	32.550	±	7.188		
Histopathology	Adenocarcinoma	28	27.089	±	9.996	1.144	0.348
	Mucinous	3	18.967	±	14.526		
	Signet ring	1	17.400	±	0.000		
	Undifferentiated	1	15.200	±	0.000		
Grade	I-II	24	26.067	±	11.844	1.276	0.301
	III-IV	9	20.188	±	11.446		
Pretreatment clinical tumor staging(cT)	T2	9	30.511	±	11.163	1.447	0.251
	T3	23	24.083	±	9.967		
	T4	1	19.500	±	0.000		
Pretreatment clinical nodal staging(cN)	N0-1	24	27.121	±	10.330	1.293	0.206
	N2	9	21.900	±	10.347		
Pretreatment clinical stage group	IIA	3	29.767	±	13.210	1.040	0.389
	IIIA	8	30.050	±	11.851		
	IIIB	18	24.172	±	9.330		
	IIIC	4	20.800	±	10.615		
Radiological Extramural vascular invasion (EMVI)	Yes	5	22.840	±	6.159	-2.176	0.146
	No	28	27.279	±	10.319		
Radiological mesorectal fascia (MRF) involvement	Positive	4	20.550	±	10.961	-1.053	0.300
	Negative	29	26.407	±	10.365		
Overall clinical down staging	Yes	15	23.227	±	10.418	0.969	0.391
	No	15	28.453	±	11.011		
	Clinical CR	3	24.267	±	5.514		
Pathological primary tumor assessment (ypT)	T0	3	24.267	±	5.514	0.445	0.775
	T1	1	23.200	±	0.000		
	T2	15	28.327	±	11.102		
	T3	13	23.662	±	11.159		
	T4	1	19.500	±	0.000		
Pathological nodal assessment (ypN)	N0-1	24	27.650	±	10.397	1.817	0.079
	N2	9	20.489	±	9.132		
Pathological stage	pCR	3	24.267	±	5.514	0.804	0.557
	I	5	24.580	±	14.617		
	IIA	2	29.100	±	14.566		
	IIIA	9	29.911	±	9.760		
	IIIB	8	26.225	±	9.981		
	IIIC	6	19.183	±	9.487		
Pathological perineural invasion (PNI)	Yes	5	16.840	±	6.159	-1.129	0.267
	No	28	20.860	±	9.245		
Pathological lymphovascular invasion(LVI)	Yes	4	26.561	±	10.557	-2.048	0.137
	No	29	27.279	±	10.319		
Presence of tumor necrosis	Partial necrosis	23	26.048	±	10.520	0.047	0.954
	No Necrosis	7	25.157	±	12.798		
	Complete necrosis	3	24.267	±	5.514		

Table 8: Overall survival and its relation to the prognostic factors.

Bujko, K., et al., (2004) compared sphincter preservation rates between SCRT with immediate surgery and CCRT with delayed surgery and reported no significant difference,[33] also there was no difference between SCRT with immediate or delayed surgery.[19] In our study, the sphincter preservation rate was 52.5%, but for patients who had low rectal tumors, the rate was 28%. Although polish trial, reported a higher sphincter preservation rate of 61%, this can be explained if we know that, they were selecting patients with no clinical evidence of sphincter involvement.[33]

Just 34 years ago, before the era of TME, postoperative RT, with anterior and posterior parallel opposed fields reduced the local recurrence (LR) from 25% to 16%,[34] with TME alone the (LR) rate declined to 11% and when preoperative CCRT was added further decline to 4.6% was achieved, patients with low rectal tumors, those with advanced tumor stage, and patients submitted to APR were found to have the highest LR rates.[35]

Dutch trial reported a two years LR rate of 2.4 % in patients treated with SCRT with immediate surgery, but most of the study patients had a low stage (patients with stage < III: 59%) and only 27% of the patients had low rectal tumors.[32]

The Swedish rectal cancer trial eventually reported that the LR rate was 9% after short-course RT with immediate surgery.[36]

In our study, the rate of LR was 9%, but it was noticed that 66.6% of the study group had low rectal tumors, and 69.7 % of them had stage III disease.

In our study, the median DFS and OS have not been reached, and the cumulative DFS at 1 year and 2 years were 88 % and 71 % respectively, while the cumulative OS at 1 year and 2 years were 90.1% and 80 % respectively.

Dutch trial showed an insignificant overall survival difference at two years between pre-operative SCRT with immediate surgery and surgery alone (82% vs. 81.8%).[32]

Bujko, K., et al., (2004) compared neoadjuvant CCRT with delayed surgery to SCRT with immediate surgery, and showed no significant difference in survival, the cumulative 4-year overall survival was 66.2% in the CCRT group vs. 67.2 % in the short-course group, and disease-free survival was 55.6%. Vs. 58.4% respectively.[14] A Randomized clinical trial compared SCRT with either immediate or delayed surgery, the 5-year survival was 63% vs. 73% but the difference was statistically insignificant, while a statistically significant increase in 5-year survival was noticed in patients who had down-staging after radiotherapy compared to patients who had no response to RT (90% vs. 60% respectively).[19]

CONCLUSION

Short-course radiotherapy with delayed surgery is a valid convenient, safe, and economically beneficial option in the management of locally advanced resectable rectal carcinoma, utilization of IMRT can help in reducing the dose to organs at risk. However, more studies with a larger number of patients are mandatory to identify the category of patients who may have the best benefit of this approach and to confirm the potential clinical benefit of using IMRT.

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